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Molecular basis of activity of 8-azapurines in transcription processes

RAJENDRA PRASAD OJHA and NITISH K. SANYAL
Department of Physics, University of Gorakhpur, Gorakhpur 273 009, India

Abstract. The quantum mechanical perturbation method has been utilized to study the biological activity of 8-azapurine (8-azaguanosine, 8-azaadenosine and 8-aza-2,6-diamino-purine) nucleoside antibiotics. The in-plane (hydrogen bonding) and stacking energy of 8-azapurine bases have been evaluated with nucleic acid bases and base pairs in all possible orientations. The energy values and the sites of association of analogous bases, obtained by optimization of energy values as well as the sites of association of nucleic acid bases during the transcription process have been compared. The model developed earlier for the incorporation of nucleoside analogues has been used to find out the inhibitory effects of the drug on nucleic acid and protein synthesis. It has been observed that the activity of 8-azapurines are of the following order

8-azaguanine > 8-aza-2,6-diaminopurine > 8-azaadenine

and these analogues show preference for binding near a guanine or cytosine in the chain. The results are in agreement with the experimental observations.

Keywords. Interaction energy; nucleoside analogues; transcription; incorporation and inhibition.

Introduction

Nucleosides play an important role in cellular metabolism, and any chemical modification brings about an alteration of the nucleotide structure as a whole. A number of synthetic and natural nucleoside analogues with interesting biological properties are known and some of them have already been successfully employed as therapeutic agents. These nucleoside analogues all share the common feature that their biological function requires an intracellular conversion to the corresponding nucleotides. Investigation of the mechanism by which these nucleoside analogues interfere with cellular metabolism, therefore, requires sufficient data on interaction with nucleic acid fragments at the molecular level. The differences in the activity between the naturally occurring bases and the modified bases are partly due to the structural changes and partly to the electronic effects brought about by the various modifications. One general class of modified bases is characterized by the sub-stitution of a N atom for a C-H group or *vice-versa.* The class includes the 8-azapurines, 6-azapyrimidines, 3-deazapyrimidine and 7-deazaadenine. Nucleosides of 8-azapurines, known as one of the orthoazanucleosides, have the interesting features that without the H atom at the ortho position, the steric behaviour of rotation of the base around the glycosyl bond is greatly reduced.

Using the model developed by Sanyal *et al.* (1981a, 1984, 1987) an attempt has been made for the first time to explain the drug action with particular reference to pyrazolopyrimidine (Sanyal *et al.,* 1986c, 1987), pyrrolopyrimidine (Sanyal *et al.,*1984), 6-azapyrimidine (Ojha *et al.,* 1988) etc. In the previous papers of this series (Sanyal *et al.,* 1980a, b, 1981a, b, 1984), the interaction of some antibiotic nucleosides with the DNA base pairs have been studied within the entire space of deep groove of the DNA double helix, using the electrostatic hard-sphere model. It was shown by computing the interaction energy and taking into account

the possible sites of association, that the possibility of incorporation of the analogous molecules instead of the normal bases during transcription can be predicted. In continuation of these studies, we have extended our computation to calculate the higher terms up to second order. In the present paper an attempt has been made to investigate the biological activity of 8-azapurines (figure 1) on the basis of our earlier model (Sanyal *et al.,* 1986a, b, 1987).

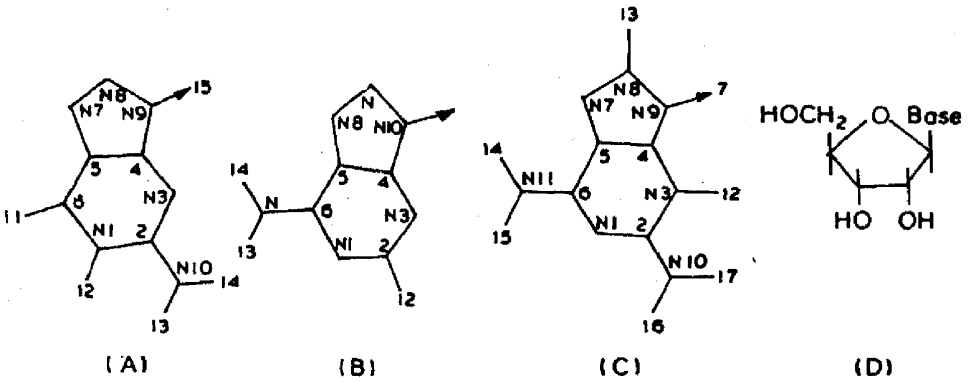

Figure 1. Chemical structure of 8-azapurines. (A), 8-Azaguanine; (B), 8-azaadenine; (C), 8-aza-2,6-diaminopurine; (D), nucleoside.

8-Azapurines (8-azaguanine, 8-azaadenine and 8-aza-2,6-diaminopurine) are important analogues of nucleic acid constituents because of their anti-neoplastic properties. The carcinostatic activities of these compounds vary substantially e.g., 8-azaguanine (Montegomery *et al.,* 1970) showing a broad range of activity while 8-aza-2, 6-diaminopurine is only moderately effective against adenocarcinoma 755 (Montegomery, 1959). 8-Azaguanine gets incorporated into nucleic acids of tumors and viruses (Mitchell *et al.,* 1950; Matthew, 1953; Smith and Matthew, 1957). Substitution of 8-azaguanine for guanine in RNA is considerable while very little substitution is possible in DNA (Mandel *et al.,* 1954). 8-Azaadenine has also been studied for its antileukemic activity (Shelley and Glayton, 1973). Experimental studies on 8-azaadenine nucleoside are limited.

The conformation (Singh and Hodgson, 1974) about axocyclic (C(4)′-C(5)′) bond is *gt* and conformation about glycosidic bond (χ_{CN}) is in the intermediate range between anti and *syn* region called high anti (Prusiner *et al.,* 1973). The NMR studies on 8-azapurine in aqueous solution show that the sugar conformation is in C(3')-endo C(2′)-endo equilibrium and the conformation about glycosyl bond is in *syn*⇌ anti equilibrium (Lee *et al.,* 1975). Ludemann *et al.* (1976) observed that the *gg* conformation is preferred over *gt* and *tg* conformations. Based on PCILO computation, Saran *et al.* (1978) have suggested that 8-azapurine nucleosides having C(2′)-endo and C(3′)-endo sugar puckering exhibit the most preferred conformation *gg* for exocyclic bond. For the glycosyl torsion angle (χ_{CN}), C(2′)-endo 8-azanucleosides prefer anti whereas C(3′)-endo nucleosides prefer *syn* conformation.

Methodology

The details of the method have already been discussed in the previous papers (Sanyal *et al.,* 1980a, b, 1981a, b, 1984, 1985b, 1986a, b, c, 1987). The crystallographic

structure of 8-azapurines and nucleic acid fragments have been taken from literature (Singh and Hudgson, 1974; Purnell and Hudgson, 1976; Singh and Hudgson, 1975; Voet and Rich, 1970). CNDO/2 method (Pople and Beveridge, 1970) has been used to compute the monopole and dipole components at the atomic centres. These molecular charges have been used to calculate the interaction energies. The total energy may be expressed as a sum of various components

$$E_{tot} = E_{el} + E_{pol} + E_{disp} + E_{rep}$$

where E_{tot} stands for the total interaction energy while E_{el}, E_{pol}, E_{disp} and E_{rep} represent the electrostatic, polarization, dispersion and repulsion energies respectively. The electrostatic component is the resultant of the sum of interactions between various atomic multipole *i.e.*, monopole-monopole, monopole-dipole and dipole-dipole. The details of the formula used may be found in the works of Caillet and Claverie (1975), Claverie (1978), Vasanth Kumar and Govil (1982) and Sanyal *et al.* (1986b, c, 1987). The minimization method (Sanyal *et al.,* 1986b, c, 1987) has been used to obtain minimum energy configuration.

Computation was carried out on CDC-Cyber 170 Computer at the National Computer Centre, Tata Institute of Fundamental Research, Bombay.

In-plane interaction energy

The in-plane interactions can be grouped into two parts, one represents the interaction with bases while the other represents interaction with base pairs.

Dimer energy

In the present case, since we are interested in the transcription and replication process and the stability of nucleic acids, the pairing energy corresponding to the position of Watson-Crick pair has been calculated. Table 1 shows the pairing energies of 8-azapurine with pyrimidine and the corresponding configurations are shown in figure 2. The pairing energies of nucleic acid bases have already been discussed in detail (Sanyal *et al.,* 1986a, b, c, 1987). The complex formed by 8-azaguanine (azaG) is stabler than the other complexes. The energy values

Table 1. Dimer energy: Hydrogen bonding energy (in kcal/mol) of 8-azapurines with pyrimidines.

Analogue	Complex formed		E_{el}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
8-Azaguanine (azaG)	azaG : C		−21·02	−3.23	−7.75	9.59	−22.41
	azaG : U		−12·13	−2·85	−5·71	6·58	−14·10
	azaG : T		−11·77	−2·83	−5·87	6·59	−13·88
8-Azaadenine (azaA)	azaA : C		−8·72	−1·31	−6·09	6·65	− 9·47
	azaA : U		−7·50	−0·92	−5·83	5·63	− 8·62
	azaA : T		−7·38	−0·91	−5·90	5·63	− 8·56
8-Aza-2,6-diaminopurine (ADAP)	ADAP : U	I	−8·89	−1·36	−7·17	7·17	−10·25
		II	−8·69	−1·39	−7·25	7·31	−10·02
	ADAP : T	I	−8·76	−1·36	−7·25	7·18	−10·19
		II	−8·74	−1·39	−7·31	7·32	−10·13

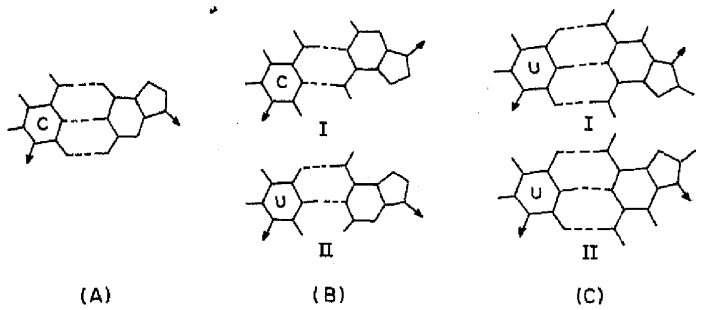

Figure 2. Dimer complexes of 8-azapurines with nucleic acid bases. (A), 8-Azaguanine; (B), 8-azaadenine; (C), 8-aza-2, 6-diaminopurine.

corresponding to azaG:U/T complexes are considerable corresponding to the energies of A: U/T pairs but they distort the nucleic acid chain and tend to restrict the elongation process. 8-Azaadenine (azaA) forms Watson-Crick pairs with U/T with the energy values comparable to A: U/T pair (–8·52/ –8·49 kcal/mol) and it forms a distorted complex (figure 2) with cytosine. The complex formed by 8-aza-2, 6-diominopurine have the energy values greater than those for the standard dimer energy for A:U/T base pairs. In figure 2, one complex will distort the chain and stops the growth of the nucleic acid, while the other is helpful in template recognition during replication process.

For all the complexes, the electrostatic component is dominant and primarily responsible for the binding of the two molecules in the positions shown in figure 2, while the polarization and dispersion terms reduce the effect of repulsion term and are eventually useful for searching the minimum energy positions.

Trimer energy

The total association energy of the analogue with the nucleic acid base pairs along with the various components of energy in the minimum energy position are shown in table 2. The minimum energy configurations corresponding to these energies are given in figure 3. The comparative studies of the site of interaction of these complexes with the standard complexes are shown in figure 4. The arrows represent the glycosyl bond of the 8-azapurine nucleoside in different configurations. The head of the arrow points towards the (Cl′) atom of sugar moity, while the tail represents the N9 atom of the azapurine base. The arrows with star-marks represent the recommended site of association in transcription process of nucleic acid bases (Sanyal *et al.,* 1986a, b,c, 1987).

Complex I is formed by the interaction of 8-azaguanine from the deep groove side of G–C base pair which bears the energy value – 22·42 kcal/mol. Complexes II and III are formed by A–U and A–T base pairs. The energy values with A–U pair are significant while the energy values with A–T pair are comparable to the (A–U)–A and (A–T)–A complexes (Sanyal *et al.,* 1986a, b,c, 1987). In figure 3A, only the complexes with A–U pairs are shown because the position of enterant analogous base is same with both A-U and A–T pairs.

8-Azaadenine forms the complexes IV–VII when it interacts with same receptor (figure 3B). The complexes IV and V represent the interaction of 8-azaadenine with A–U and A–T pair while VI and VII represent the complexes with G-C pair. The

Table 2. Trimer energy: Hydrogen bonding energy (in kcal/mol) of 8-azapurines with nucleic acid base pairs.

Enterant base	Base pair	E_{el}	E_{pol}	E_{disp}	E_{rep}	E_{tot}	Complex
azaG	G–C	−20·74	−3·44	−7·93	9·69	−22·42	I
	A–U	−9·00	−2·50	−8·70	9·15	−11·07	II
		−3·36	−1·32	−6·00	4·91	−5·75	III
	A–T	−5·59	−1·67	−7·69	6·03	−8·83	II
		−3·50	−1·34	−6·02	4·94	−5·92	III
azaA	A–U	−4·45	−0·89	−6·28	5·91	−5·71	IV
		−2·40	−0·86	−5·71	5·45	−3·61	V
	A–T	−4·34	−0·86	−6·51	5·91	−5·79	IV
		−2·54	−0·87	−6·75	5·45	−3·71	V
	G–C	−8·99	−1·83	−5·64	5·74	−10·63	VI
		−0·72	−1·31	−5·06	3·32	−3·77	VII
ADAP	G–C	−7·65	−1·33	−7·19	6·94	−9·23	VIII
		0·40	−1·96	−6·50	4·98	−3·07	IX
	A–U	−4·58	−1·45	−7·72	6·71	−7·05	X
		−3·03	−1·23	−7·36	6·76	−4·86	XI

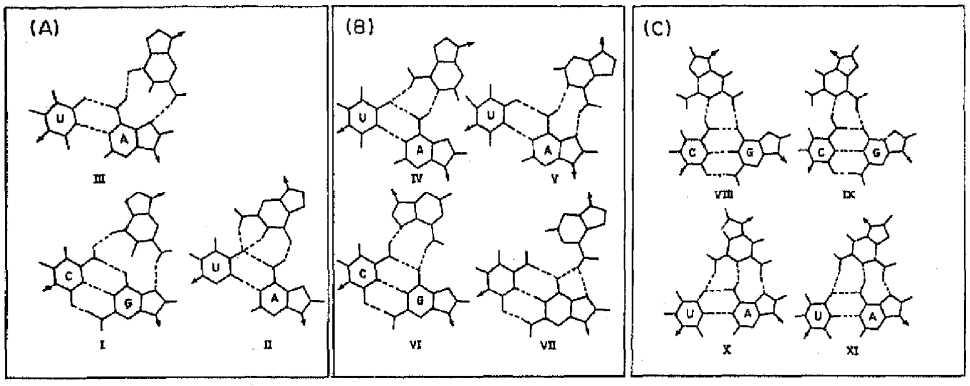

Figure 3. Minimum energy configurations formed by 8-azapurine with nucleic acid bases. (A), 8-Azaguanine; (B), 8-azaadenine; (C), 8-aza-2,6-diaminopurine.

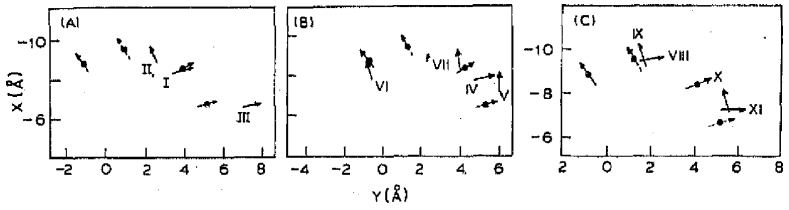

Figure 4. Arrow diagram corresponding to the sugar ends of the enterant analogue in the minimum energy configuration of base pair interaction. The arrows with asterisk represent the recommended site of interaction. The origin is considered at the N1 atom of purine in the base pair and the X-axis along the N1-C2 bond. (A), 8-Azaguanine; (B), 8-azaadenine; (C), 8-aza-2,6-diaminopurine.

energy value for complex IV is comparable to the energy value of (A–U/T)–A complex while the other complexes have lesser energy values than the recommended energies (Sanyal *et al.,* 1986a,b,c, 1987).

Two complexes VIII and IX are formed by interaction of 8-aza-2,6-diaminopurine base from the deep groove side of G–C base pair, as shown in table 2 and figures 3C and 4C. The two complexes bear the energy values – 9·25 kcal/mol and – 3·07kcal/mol respectively. The magnitude of energy values for these complexes are smaller than (G–C)–G and (G–C)–C complexes recommended for incorporation of nucleosides during transcription process (Sanyal *et al.,* 1986a, b, 1987). The trimer complexes formed by A–U pair are X and XI with energy values – 7·05 kcal/mol and 4·86 kcal/mol respectively are reported in table 2, while the corresponding minimum energy configurations are shown in figure 3C. These energy values are comparable to the energy values for (A–U)–A and (A–T)–A complexes (Sanyal *et al.,* 1986a, b,c, 1987).

The stability of the complexes for the 8-azapurines can be represented as

I >II >III	for 8-azaguanine
VI >IV>VII>V	for 8-azaadenine

and

VIII >X >XI >IX	for 8-aza-2,6-diaminopurine

and the electrostatic terms are primarily responsible for their binding.

It is clear from figure 4A that the site of interaction corresponding to complex I is the same as that recommended for transcription. The corresponding energy value is more than the energy value of (G–C)–G complex (–20·91 kcal/mol). The complex II has energy value more than the (A–U/T)–A complexes (–5·01/–4·42 kcal/mol), but the site of association is displaced from the recommended site of association and also has an angular deviation. The complex III has energy value similar to the recommended energy value but the site of association is again displaced from the recommended site. From this discussion it is clear that, only complex I is suitable for transcription energywise and also in terms of spatial position.

In case of 8-azaadenine there are four complexes IV-VII, two (IV, V) for interaction with (A–U)/(A–T) pairs and the other two (VI, VII) for interaction with the G–C pair. It is found that the complex IV with energy value –5·71/–5·79 kcal/mol is suitable for binding in the deep groove during the transcription process. Complex V with A–U/A–T pairs having energy value –3·61/–3·71 kcal/mol has lower energy value than the recommended energy values. The site of interactions for these complexes are illustrated in figure 4B. Complex IV is slightly displaced from the star-marked arrow (which represent the recommended site), while the arrow corresponding to complex V is appreciably displaced from the recommended site and also has an angular deviation. A comparison of energy values of VI and VII complexes (table 2) and the site of association shown in figure 4C with recommended (star-marked) sites, show that they have energy values lower than the energy values for the (G–C)–G complex and therefore, binding is not possible. The arrows corresponding to these complexes (VI and VII) are considerably displaced and deviated in varying degrees with respect to recommended site. Therefore, it is inferred that the binding of 8-azaadenine is not possible at the probable sites of association, but their binding as represented by complex IV with A–U pair and complex VI with G–C pair cannot be totally ruled out. Since the association site for complex IV is displaced, it may be postulated that it may attain the predicted site with minor decrease in their binding energy. In other words, it requires some

additional amount of energy to place the complex at the specified site (Sanyal *et al.,* 1986a, b,c, 1987). This additional energy can be made available in the system due to conversion of ATP to AMP and also due to the presence of some enzymes (Stent, 1971; Watson 1970; Saenger 1984). Saran *et al.* (1978) have suggested that for 8-azaadenine the energy difference between its conformation from *gg* to *gt* and *tg* for C(4′)-C(5′) bond is 1 kcal/mol, while it requires 0·5–1 kcal/mol energy to change the conformation from anti→ *syn* for χ_{CN}. The binding through these complexes requires appreciable additional energy which may easily alter the conformation from anti→*syn*. This restricts the incorporation of 8-azaadenine during transcription process.

8-Aza-2, 6-diaminopurine forms 4 complexes VIII-XI, two (VIII and IX) with G-C pair and other two (X and XI) complexes with A– U pairs. As shown in figure 4C, the complex VIII is widely devited and displaced from the recommended site while the complex IX is slightly displaced from the standard position (arrows with asterisk). The energy value for (G–C) –ADAP is less than the recommended energy values for (G–C)–G and (G–C)–C complexes as reported earlier (Sanyal *et al.,* 1986a, b, c, 1987). It may be inferred that none of the complexes with G– C pair satisfy the condition for the incorporation of the analogue during transcription process. The spatial position of complex X (figure 4C) is slightly displaced, while there is very little deviation from the recommended site of association. The complex XI is appreciably displaced and deviated from the standard site of association. This complex may be displaced to the recommended site. In this process some of the association energy has to be reduced from its earlier value (reported in table 2) which is greater than the recommended energy for (A–U)–A complex. Therefore, in drastic conditions the binding through the complex X is possible during the transcription process.

The conformational requirement for the incorporation of analogue is *gg* and anti (Sanyal *et al.,* 1981a, 1984, 1986a,b,c, 1987; Ojha *et al.,* 1988). As discussed earlier, anti⇌*syn* equilibrium exists in 8-azaguanine, which permits the incorporation of 8-azaguanine. It is therefore, inferred that 8-azaguanosine can effectively substitute for guanosine during transcription process while the incorporation of 8-azaadenine is not possible. However, 8-aza-2,6-diominopurine may incorporate in the chain through complex X only to some extent. The incorporation of nucleoside analogues for normal bases in the RNA chain, produces miscoding in the nucleic acid chain. As a result, the inhibition of protein synthesis takes place.

Levin (1963) observed that a major amount of 8-azaguanine is incorporated into the tRNA, and the analysis of the tRNA containing 8-azaguanine revealed that only guanine residues are replaced by the analogue and that the nucleotide sequence is not otherwise altered (Weinstein and Grunberger, 1965). This is in agreement with our results. This analogue containing tRNA does, however, appear to function normally despite the fact that one might predict apriori that slight alteration in the structure of tRNA might alter the specificity so that miscoding would result. (Weinstein and Grunberger, 1965; Levin, 1965). This is in agreement with our results, as discussed earlier, due to incorporation of 8-azaguanine in place of guanine resulting in the change of codons. In the same way, it is easy to explain from our results that 8-azaguanine is incorporated in to mRNA as observed experimentally (Levin, 1966; Grunberger and Mandel, 1965; Grunberger *et al.,* 1964, 1968). Nevertheless, the presence of 8-azaguanine causes production of abnormal

RNA (Otaka *et al.,* 1961) and accompanying rapid decrease in protein synthesis (Mandel, 1958). Roy *et al.* (1961) have suggested that since the mRNA and tRNA are apparently functional, the inhibition of nucleic acid is not by the 8-azaguanine polyphosphate, but due to other factors. The binding of the analogue in the presence of enzymes (or other suitable experimental conditions), when some extra source of energy is available, indicate that it can stop the growth of the template (due to conversion of anti→ *syn* in the presence of energy) resulting in the inhibition of nucleic acid synthesis (through complex II). The use of 8-azaadenosine as anti-leukemic is due to its binding in the template in the presence of required energy, resulting in the inhibition of the growth of the nucleic acid template. The effectiveness of 8-aza-2,6-diaminopurine against adenocarcinoma 755 (Montegomery, 1959) is thus explained (through inhibition of DNA, RNA or protein synthesis).

Stacking energy

The stacking energy of 8-azapurines with nucleic acid bases (G, C, A, U and T) are shown in table 3 while their corresponding minimum energy configurations are shown in figure 5. The relative effect of the energy components (electrostatic, polarization, dispersion and repulsion) are given in table 3. The stacking energy represent the stability of the stacked complexes. One can conclude that the stability of these complexes are in the following order for 8-azapurines:

$$\binom{\text{azaG}}{\text{G}} > \binom{\text{azaG}}{\text{C}} > \binom{\text{azaG}}{\text{A}} > \binom{\text{azaG}}{\text{U}} > \binom{\text{azaG}}{\text{T}}$$

for 8-azaguanine,

$$\binom{\text{azaA}}{\text{C}} > \binom{\text{azaA}}{\text{G}} > \binom{\text{azaA}}{\text{U}} > \binom{\text{azaA}}{\text{T}} > \binom{\text{azaA}}{\text{A}}$$

Table 3. Stacking energy (in kcal/mol) of 8-azapurine with nucleic acid bases.

Enterant analogue	Enter-acting base	E_{el}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
azaG	G	−14·32	−3·32	−6·90	3·22	−21·32
	C	−9·83	−2·59	−5·20	1·91	−15·70
	A	−6·71	−1·57	−7·16	3·42	−12·02
	U	−4·15	−1·92	−6·41	2·19	−10·29
	T	−4·29	−1·71	−5·45	1·42	−10·23
azaA	G	−7·07	−1·58	−7·92	4·46	−12·11
	C	−7·49	−1·45	−6·65	3·26	−12·33
	A	−3·80	−0·51	−7·25	3·40	− 8·16
	U	−5·11	−0·93	−5·68	2·43	− 9·29
	T	−4·78	−0·96	−5·91	2·54	− 9·10
ADAP	G	−14·21	−3·95	−14·48	10·47	−22·14
	C	−15·50	−5·30	−10·41	6·52	−24·70
	A	−9·26	−2·44	−11·29	6·74	−16·25
	U	−7·61	−3·00	−11·41	7·46	−14·56
	T	−8·60	−4·04	−10·35	6·24	−16·76

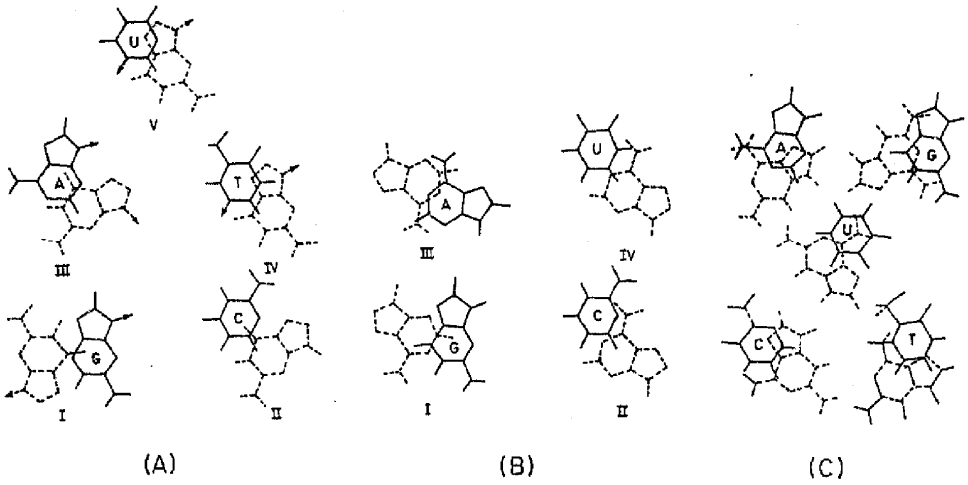

Figure 5. Stacked complexes of 8-azapurine, (A), 8-Azaguanine; (B), 8-azaadenine; (C), 8-aza-2,6-diaminopurine.

for 8-azaadenine and

$$\binom{\text{ADAP}}{\text{C}} > \binom{\text{ADAP}}{\text{G}} > \binom{\text{ADAP}}{\text{T}} > \binom{\text{ADAP}}{\text{U}} > \binom{\text{ADAP}}{\text{A}}$$

for 8-aza-2,6-diaminopurine.

It is inferred that 8-azapurines prefer to bind in the neighbourhood of the dipolar bases guanine or cytosine during the template recognition. The stacking energy considerations and the conformational requirements of the nucleotides indicate that the selection of the specific site of these analogues for the binding near guanine or cytosine depends on the selection of the particular chain of DNA on which the new template is formed in the transcription process.

Conclusion

The interaction energy studies on 8-azapurines show that 8-azaguanine can easily be incorporated in the transcription process through configuration I. The incorporation of 8-azaguanosine in the RNA chain, for guanosine, alters the specificity so that miscoding results. The production of abnormal RNA due to its incorporation rapidly decreases the rate of protein synthesis which is in agreement with the experimental results. 8-Azaadenosine cannot be incorporated in the RNA chain but it may bind during the elongation process and stop the growth. 8-Aza-2, 6-diaminopurines are moderately incorporated in the chain and binds during the elongation process to inhibit the protein and nucleic acid synthesis. 8-Azapurine prefers to bind near guanine or cytosine and selection of these complexes depends on the consideration of the template. These properties are perhaps responsible for the carcinostatic activities of the drugs. This study offers a mechanism for the activity of the nucleoside antibiotic. The activity of 8-azapurines are of the following order

8-azaguanine > 8-aza-2,6-diaminopurine > 8-azaadenine.

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